Remarks

Status of Claims

Applicants acknowledge that claims 1-3, 12, 16, 42, 43, 72, 74-78, 81, 82, 84-88, 91, 92, 94, 95, 106, 108, and 110-114 were pending and under examination. Claims 1-3, 42, 43, 72, 74, 75, 82, 84, 85, 92, 94, 95, 111, 113 and 114 have been canceled. Applicants have amended claims 12, 16, 76, 78, 81, 86, 88, 91, 106, 108, 110, and 112. New claims 115-123 are added. Thus, claims 12, 16, 76-78, 81, 86-88, 91, 106, 108, 110, 112, and 115-123 are pending and under examination.

Claims 78, and 88 were amended to change the format of a dependent claim to an independent claim, incorporating all of the limitations of the claim from which it originally depended.

Claims 12 and 81 were amended to add the word "isolated".

Claim 91 was amended to add the phrase "a pharmaceutically acceptable carrier".

Claims 12, 16, 76, 81, 86, 91, 110, and 112 were amended to delete the phrase "or viral mRNA" in accordance with the finality of the restriction requirement.

Claims 12, 16, 76, 81, 86, 91, 110, and 112 have been amended to recite that the claimed isolated RNA is in the form of two separate strands. Support for the amendment is found in the specification on page 2 lines 21-22. The claims have also been amended to remove the term "about".

New claims 115-123 have been added. New claims 115-117 particularly recite the length of the claimed isolated RNA as being 21, 22, or 23 nucleotides. Support for each of these limitations is found within the originally claimed range of about 21 to about 23 nucleotides. New claims 118-123 depend from claims 110 and 112 and recite various limitations previously presented in, for example, claims 77, 87, 81, 87, and 108, as well as particularly reciting the length of the claimed isolated RNA as being 21, 22, or 23 nucleotides.

Support for the new claims can be found throughout the specification and claims, as originally filed. No new matter has been added.

Interview

Applicants thank Examiners Wollenberger, McGarry, and Schultz for conducting a personal interview with Applicants and Applicants' representatives. Issues related to the rejections under 35 USC 112 and 102 as set forth in the Office Action were discussed. Applicants also pointed out that paperwork had been submitted by one co-owner relating to the priority claim. An issue related to priority was raised in the IDS filed July 7, 2005.

Location of Application

Applicants acknowledge that the location of the application has changed and that the application is now located in Art Unit 1635 and has been docketed to Examiner Louis V. Wollenberger.

Response to Election

Applicants acknowledge the finality of the restriction requirement on the grounds that it would be burdensome to search the entire claim reciting both cellular and viral mRNA together. Although Applicants disagree, the claims have been amended in order to advance prosecution.

Continued Examination Under 37 CFR 1.114

Applicants acknowledge the acceptance of the submission for continued examination and the withdrawal of the previous Office Action pursuant to 37 CFR 1.114.

Double Patenting

The Examiner has provisionally rejected claims 1-3, 12, 16, 42, 43, 72, 74-78, 81, 82, 84-88, 91, 92, 94, 95, 106, and 108, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 7, 8, 13, 14, 20, 25, and 27 of co-pending Application No. 10/255,568, and over claims 1, 3, 4, 7, 8, 11, 12, 13, 14, 27 and 28 of co-pending Application No. 11/142,866. Claims 1-3, 42, 43, 72, 74-75, 82, 84-85, 92, 94, and 95 of

the instant application have been canceled rendering the rejection moot with respect to these claims. Regarding the remaining pending claims, Applicants submit the following.

Applicants respectfully direct the Examiner's attention to the fact that a Response to Restriction Requirement was filed by Applicants in the commonly-owned, co-pending Application No. 10/255,568. Following election, claims 1, 4, 7, 8, 13, 14, 20, and 27 of Application No. 10/255,568 are withdrawn from consideration. Claim 20 is subject to rejoinder with the elected claims. Applicants intend to cancel non-elected claims, for example, claims 1, 4, 7, 8, 13, 14, and 27, in Application No. 10/255,568 in due course. Accordingly, only claims 20 and 25 of co-pending Application No. 10/255,568 remain relevant to the instant provisional double patenting rejection. Claims 20 and 25 of co-pending Application No. 10/255,568 are directed to methods of mediating RNA interference using RNAi-mediating compositions (i.e., method claims). The claims of the instant application are, in contrast, directed to RNA interference-mediating compositions (i.e., composition of matter claims). Applicants note that in both the instant case and in co-pending Application No. 10/255,568 the Patent Office restricted the method of treatment claims and composition of matter claims as being directed to patentably distinct inventions. Accordingly, Applicants submit that the instant provisional double patenting rejection in view of claims of co-pending Application No. 10/255,568 is inappropriate.

Applicants further note that co-pending Application No. 10/255,568 has not yet undergone substantive examination. Applicants understand that in accordance with Section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner until the "provisional" double patenting rejection is the only rejection remaining in one of the applications. Should the instant claims be found allowable and Applicants be unable to overcome any remaining provisional obvious-type double patenting rejection in co-pending a-Application No. 10/255.568, Applicants will consider filing of a terminal disclaimer in the later-filed case to overcome the rejection.

With regards to Application No. 11/142,866, Applicants note that the application has not yet undergone substantive examination. Applicants submit that a provisional obviousness-type double patenting rejection should also be made in the conflicting application. As the Examiner is

aware, if provisional obviousness-type double patenting rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the rejection in the earlier filed application, *i.e.*, the instant case, thereby permitting that application to issue as a patent. The examiner should maintain the double patenting rejection in the other application as a "provisional" double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent.

Claim Objections

The Examiner has objected to claims 1-3, 12, 16, 42, 43, 72, 74-78, 81, 82, 84-88, 91, 92, 94, 95, 106, 108, and 110-114 as being drawn to a non-elected invention: RNA targeting viral mRNA. Claims 1-3, 42, 43, 72, 74-75, 82, 84-85, 92, 94, 95, 111, and 113-114 have been canceled rendering the objection moot with respect to these claims. Applicants have amended the remaining pending claims as appropriate.

Claims 72, 74, 75, 84 and 92 are objected to for grammatical issues. Applicants have canceled claims 72, 74, 75, 84 and 92, rendering the objection moot.

Claims 3, 78 and 88 are objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants traverse the Examiner's objection, but in order to expedite prosecution of the instant application claims 78 and 88 have been amended and rewritten in independent form. Claim 3 has been canceled.

Claim Rejections – 35 USC 112

Claims 12, 91, 110 and 112 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Claim 12 has been amended to correct the antecedent basis issue.

The Examiner has rejected claims 110 and 112 because they contain the phrase "one or more" "non-standard nucleotides". The Examiner has taken the position that the phrase "one or

more" has no upper limit and is therefore indefinite. In addition, the Examiner alleges that the lack of clear definition of the term "non-standard nucleotides" in the specification renders the claims indefinite. Applicants respectfully traverse.

As discussed in the interview, the skilled artisan at the time of filing of the instant application would have had a clear understanding of the meaning of the phrase "non-standard nucleotides. For instance, the skilled artisan would have appreciated that "non-standard nucleotides" are those which are not routinely found in naturally occurring polynucleotide molecules, for example, nucleotides having non-standard bases, etc. Non-standard nucleotides were well-known in the art at the time of Applicants' filing and were routinely used in DNA and RNA based methods. For instance, examples of these types of nucleotides had been used in the antisense field for years. It is not required for Applicants to include an extensive list of known non-standard nucleotides (non-naturally occurring nucleotides) in the specification in order to define the phrase "non-standard nucleotides"; its metes and bounds are understood in the art.

Furthermore, many studies have confirmed, as was taught by Applicants, that the use of one or more non-naturally occurring nucleotides in RNA of about 21 to about 23 nucleotides in length is effective for accomplishing RNA interference. Examples of these studies are found in the following references, copies of which were included in the IDS filed on March 8, 2006:

Chiu YL, Rana TM. siRNA function in RNAi: a chemical modification analysis. RNA. 2003 Sep; 9 (9):1034-48;

Elmen J, Thonberg H, Ljungberg K, Frieden M, Westergaard M, Xu Y, Wahren B, Liang Z, Orum H, Koch T, Wahlestedt C. Locked nucleic acid (LNA) mediated improvements in siRNA stability and functionality. Nucleic Acids Res. 2005 Jan 14 2005;33(1):439-47;

Braasch DA, Jensen S, Liu Y, Kaur K, Arar K, White MA, Corey DR. RNA interference in mammalian cells by chemically-modified RNA. Biochemistry. 2003 Jul 8;42(26):7967-75;

Allerson CR, Sioufi N, Jarres R, Prakash TP, Naik N, Berdeja A, Wanders L, Griffey RH, Swayze EE, Bhat B. Fully 2'-modified oligonucleotide duplexes with improved in vitro potency and stability compared to unmodified small interfering RNA. J Med Chem. 2005 Feb 24;48(4):901-4;

Czauderna F, Fechtner M, Dames S, Aygun H, Klippel A, Pronk GJ, Giese K, Kaufmann J. Structural variations and stabilising modifications of synthetic siRNAs in mammalian cells. Nucleic Acids Res. 2003 Jun 1;31(11):2705-16; and

Elbashir SM, Martinez J, Patkaniowska A, Lendeckel W, Tuschl T. Functional anatomy of siRNAs for mediating efficient RNAi in Drosophila melanogaster embryo lysate. EMBO J. 2001 Dec 3;20(23):6877-88 .

These references demonstrate that those of ordinary skill understand what non-standard nucleotides are, and their relevance in relation to the present invention.

Moreover, Applicants respectfully submit that the Examiner's assertion that the phrase "one or more" is indefinite is misplaced.

The term "one or more" is not per se indefinite. A search of the USPTO web site patent database for the term "one or more" in the claims identifies 226,224 issued US Patents (copy of search results attached hereto as Exhibit 1). A related search of the terms "one or more" and "DNA" both in the claims to reflect DNA related biotechnology inventions identified 3,221 issued US Patents. (copy of search results attached hereto as Exhibit 2). These exhibits illustrate that the USPTO well recognizes that "one or more" can be definite when used in claims, and in particular when used in claims directed to nucleic acids as in the present case. Applicants submit that the phrase as used in the instant claims is clear. The claims, as amended, are directed to RNA interference-mediating molecules that are double-stranded and 21-23 nucleotides in length. Accordingly, the phrase "one or more" has a clear lower and a clear upper limit. The Examiner appears to suggest that at the upper limit, the phrase becomes unclear because the nucleotides could be, for example, all modified nucleotides or all deoxyribonucleotides. Applicants submit, however, that the skilled artisan can easily recognize when a molecule no longer represents RNA. For example, all ribonucleotides might be modified ribonucleotides and the molecule would represent RNA, whereas if all nucleotides were deoxyribonucleotides, the molecule would be recognized as not representing RNA. Applicants further note that the pending claims recite that the RNA compositions mediate RNA interference. Accordingly, the skilled artisan would recognize that molecules within the scope of the claims would retain

sufficient RNA structural properties to function as claimed. In view of the above, Applicants respectfully request withdrawal of the rejection of claims 110 and 112 as indefinite.

Claim 91 has been amended to recite more than one component of the claimed composition.

Claim 113 has been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The Examiner has taken the position that the original limitation of "about 23" doesn't encompass the new limitation of "about 24" and that therefore the limitation "about 24" presents new matter. The Applicants traverse.

In order to advance prosecution, applicants have amended the claims to limit the length of the claimed RNA to 21-23 nucleotides. Claim 113 has been canceled.

However, applicants wish to note that they disagree with the rejection for the following reasons. It would have been clear to one of ordinary skill in the art at the time of the invention that a nucleotide length of "about 23" includes lengths of 22 or 24 nucleotides. The term "about 23 nucleotides" must encompass 24 nucleotides and 22 nucleotides or the phrase would be meaningless. There are no partial nucleotides. Thus it would have been clear to one of skill in the art that one whole nucleotide on either side of a length of 23 would be encompassed by the term "about". Therefore, the introduction of the limitation of "24' does not represent introduction of new matter.

Applicants are entitled to a claim directed to an isolated RNA of about 21 to about 23 nucleotides in length, as well as 20 and 24 nucleotides in length. Applicants will pursue such subject matter in a continuation application.

Claims 43, 81 and 91 have been rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The Examiner has relied on numerous quotes of post-filing art to argue that the instant application provides limited guidance and working examples and therefore the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention.

Claim 43 has been canceled.

Applicants first wish to state that it is unclear where the Examiner finds the requirement to examine the enablement of the therapeutic utility of the instant claims which are composition of matter claims. The claimed pharmaceutical compositions have utility in any pharmaceutical (i.e., physiological) application, for example, in cell based applications featuring live cells, as well as in in vivo application, for example, experimentation and testing in animal models, etc. All that is required of the claimed pharmaceutical compositions is that they comprise the claimed RNA interference-mediating molecules and a pharmaceutically acceptable carrier, i.e., a physiologically acceptable carrier. The claims do not recite any therapeutic use and examination of the enablement of such uses in inappropriate.

However, in order to be fully responsive, Applicants submit the following arguments with respect to the merits of the Examiner's statements of record. The Examiner has relied on art that is not relevant, Gerwitz et al., and Jen et al., deal with antisense technology which is quite different from the instant invention, namely RNAi technology. Most pertinent, antisense technology relies on the use of antisense or reverse complementary oligonucleotides that once introduced into a cell form Watson-Crick base pairs with the targeted gene's mRNA. The issues of delivery and cellular stability of antisense oligonucleotides has been well documented, including the reviews cited herein and it has been one of the major reasons for the relatively limited success of the technology for therapeutic purposes. Because RNAi functions by a different cellular mechanism and it employs double stranded RNA it does not suffer from the same delivery problems as antisense technology.

The teachings of Lu et al., Samarsky et al., Sioud et al., and Simeoni et al., are directed to RNAi technology but they are erroneously relied upon by the Examiner. Aside from the quotes by the Examiner, large portions of these teachings actually illustrate examples of successful therapeutic applications of RNAi technology including both, local and systemic delivery of siRNA into tumor, liver, ocular tissue, pulmonary tissue, brain, skin, joint and muscle. It is correct that these reviews also identify the area where improvements in the technology are needed. Like any other nascent technology, RNAi too, presents many opportunities for improvements and development, and although many improvements and alternative delivery

strategies have been developed since the invention was made by the Applicant, the invention can be practiced as claimed and described in the instant application.

Under 35 U.S.C. §112, first paragraph, the Examiner has the "initial burden of setting forth a reasonable explanation as to why the scope of protection provided by [the claims] is not adequately enabled by the description of the invention provided in the specification." In re Wright, 999 F.2d 1557 (Fed. Cir. 1993). Specifically, in In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995), it was held that:

> Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

Additionally, the court stated that in the absence of a reason to doubt the objective truth of the teachings contained in the specification, the methods of making and using the claimed invention must be taken as complying with the requirements of §112, first paragraph. Moreover, in order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See In re Wands, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. In re Wands, supra.

Claims 110-112 and 114 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. Claims 110-112 include the limitation that the isolated RNA includes one or more "non-naturally occurring nucleotides or deoxyribonucleotide or non-standard nucleotides." The Examiner has taken the position that the limitation "one or more" has no upper limit and therefore it contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention.

Claims 111 and 114 have been canceled.

The specification provides sufficient guidance to allow one of ordinary skill in the art to make and utilize the claimed nucleic acids containing one or more non-naturally-occurring or non-standard nucleotides. As mentioned above, those of skill in the art know what these non-standard nucleotides are and how to insert them into a nucleic acid. The claimed nucleic acids are not thousands of bases in length. They have an upper size limit of 23 nucleotides. One of skill in the art would appreciate how to make and use one or more non-naturally-occurring or non-standard nucleotides in the context of an about 23 nucleotide RNA.

Applicants have asserted that multiple modified nucleotides can be inserted into the claimed RNA and still work in the process of RNA interference. Several published reports confirm these assertions. In particular, the Chiu and Rana reference mentioned above describes a study in which a number of modified nucleotides could be inserted into the RNA without destroying the activity of the molecule.

Additionally, not every modified nucleotide combination must work equivalently or even work at all in order for the claims to be enabled. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 1984 (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude…possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." "The mere possibility a composition claim embraces inoperable species or a process claim embraces inoperable reactants does not render it unduly broad." *In re Kamal et al.* (CCPA1968) 398 F2d 867, 158 USPQ 320.

Claim Rejections – 35 USC 101

The Examiner has rejected claim 12 under 35 USC 101 as being directed to non-statutory subject matter. Applicants respectfully submit that the pending claim clearly indicates the presence of the hand of man, however, in order to advance prosecution, Applicants have added

the term "isolated" to claim 12. It is believed that the amendment is sufficient to overcome the rejection.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 2, 3, 12, 16, 86, 87, 88, 106, 108, and 110-114 are rejected under 35 USC 102(b) as being anticipated by Wu et al., (1998) J. Biol. Chem. 273:2532-2542.

Wu et al. teach 17-mer modified oligonucleotides targeting human Ha-Ras mRNA for use in antisense therapeutics. Applicants respectfully traverse. The rejection is moot in view of Applicants amendments to the claims. The RNA described by Wu et al. is not encompassed by the claimed molecules. Therefore, a rejection of the instant claims under 102(b) over Wu et al. is inappropriate.

Claims 1-3, 12, 16, 43, 72, 74-78, 81, 86-88, 91, 92, 94, 95, 106, 108, 110-114 are rejected under 35 USC 102(b) as being anticipated by Szyf et al. (US Patent 5,578,716), as evidenced by Zhang et al. (2004) Cell 118:57-68. Applicants respectfully traverse.

Szyf et al. teach antisense oligonucleotides that are complementary to mRNA or double stranded DNA that express DNA methyl transferase. The antisense oligonucleotides described in the fifth embodiment of Szyf et al (column 6-7) are self-complimentary "hairpin" oligonucleotides for inhibiting mammalian DNA MeTase mRNA. The antisense oligonucleotides described in the third embodiment of Szyf et al (columns 5-6) are chimeric oligonucleotides having DNA regions and RNA regions.

The Examiner has rejected Applicants RNA claims based on two teachings in Szyf et al: the third embodiment of Szyf et al which describes a chimeric DNA-RNA oligonucleotide and the fifth embodiment which describes hairpin structures which have some double stranded components. Applicants have amended the claims to limit the double stranded RNA to RNA in the form of two separate strands of RNA which form an RNA duplex rather than a single strand which forms a hairpin structure. Szyf et al does not describe a duplex of RNA composed of two

separate strands, each strand having a size of 21 to 23 nucleotides. In view of the amendments to these claims, it is requested that the rejection be withdrawn.

The Examiner also takes the position that the vector constructs of Szyf's Example 1 used to introduce the antisense oligonucleotides in the cell can be ultimately processed by the endogenous ribonuclease Dicer to fragments of about 15-21 nucleotides. Initially, Applicants disagree that the pZαM or pZEM constructs would be processed to produce RNA of about 21 to about 23 nucleotides. It is unclear if this rejection is being applied to DNA claims 72 and 74-75 or RNA claims 1-3, 43, 76-78, 81, 86-88, 91, 106, 108, and 110-114. If the rejection is directed at DNA claims 72 and 74-75, Applicants have canceled these claims.

If the rejection is directed at the RNA claims, the issue of how the material is processed in the cells is not relevant. Each of claims 1-3, 43, 76-78, 81, 86-88, 91, 106, 108, and 110-114 are directed to *isolated* RNA and not RNA produced inside cells that remains within the cells. An isolated RNA is one which is produced synthetically, recombinatly or naturally but which is separated from the components with which it normally exists in nature. Thus, even if the vectors of example 1 produced double stranded RNA of about 21 to about 23 nucleotides in length within a cell it would not be *isolated* RNA. The issue of *Schering Corporation v. Geneva,* as discussed with the Examiners in the interview, is discussed further below with respect to the rejection in view of Fire et al.

Claims 1-3, 12, 16, 43, 76, 77, 78, 81, 86-88, 91, 106, 108, 110-114 are rejected under 35 USC 102(b) as being anticipated by Agrawal et al. (WO 94/01550). Applicants respectfully traverse.

Agrawal et al. teach single stranded antisense self-stabilized, hairpin DNA oligonucleotides that form stable DNA:target mRNA duplexes, resist nucleolytic degradation and activate RNaseH, for inhibiting gene expression in cells and animals.

Each of the pending claims, as amended is directed to isolated double stranded RNA having two separate strands of RNA which form an RNA duplex rather than a single strand which forms a hairpin structure. Agrawal et al do not describe a duplex of RNA composed of

two separate strands, each strand having a size of 21 to 23 nucleotides. In view of the amendments to these claims, it is requested that the rejection be withdrawn.

Claims 1-3, 43, 81, 86-88, 91, 106, 108, 110-114 are rejected under 35 USC 102(e) as being anticipated by Crooke (US Patent 6,107,094).

Crooke discloses chemically modified oligomeric compounds which "have certain RNA like features that allow them to form a double stranded structure with a targeted RNA region and this double stranded structure is subsequently degraded by eukaryotic dsRNases." (paragraph spanning columns 9 and 10). The oligomeric structures with RNA features are single stranded molecules. They form double stranded molecules with target RNAs under test conditions in a cell or test solution. The only actual duplexes described by Crooke are the ones identified by the Examiner in Table 1 (17 mer and 20 mer).

Throughout the rejection the Examiner has referred to the teachings about duplexes or double stranded RNAs, ie., related to chemical synthesis modification of backbones etc. Applicants wish to clarify for the record that Crooke is actually referring to single stranded molecules. When Crooke refers to double stranded molecules it is in the context of the RNA oligomers bound to a target molecule. Thus in the sections regarding chemical synthesis and backbone modifications, Crooke is actually referring to single stranded molecules. His duplex molecules would not have modified nucleotides or backbones on the target RNA strand because the target is made by the cell with the exception of the four duplexes synthesized (artificial substrates) in Example 27a for analysis of the enzyme in a solution ie. Table 1.

Regardless, the rejection is moot in view of Applicants amendments to the claims. The RNA described by Crooke et al. is not encompassed by the claimed molecules. Therefore, a rejection of the instant claims under 35 USC 102 over Crooke et al. is inappropriate.

Claims 1-3, 12, 16, 42, 43, 72, 74-78, 81, 82, 84-88, 91, 92, 94, 95, 106, 108, 110-114 are rejected under 35 USC 102(e) as being anticipated by Fire et al. (US Patent 6,506,559), as evidenced by Meister et al. (2004) Nature 431:343-349.

The Examiner has stated that "the claims are directed to double stranded RNAs that are 15-21 nucleotides in length that specifically inhibit the expression of a mammalian target gene wherein one strand is complementary to less than the full-length of a target gene." It is unclear which claim the Examiner is referring too. He is respectfully request to clarify this issue.

Fire et al teach nucleic acids of length of at least 25 nucleotides that mediate RNAi. In contrast, the present claims, as amended, are limited to nucleic acids that are 21-23 nucleotides in length. The Examiner has asserted that the RNA of Fire et al is cleaved to dsRNA duplexes of 21-23 nucleotides within the cell and that such a process inherently anticipates Applicants claimed invention. Applicants disagree.

Each of the pending claims is directed to isolated double stranded RNA. Even if the RNA that is produced by the cells described in Fire et al were to have a length of 21-23 nucleotides, which Applicants do not concede, the disclosure would not inherently anticipate the claimed invention. Applicants claims are directed to isolated RNA. The RNA produced by a cell or cell extract is not isolated RNA. Thus, the claims are novel in view of Fire et al in view of Meister et al.

The *Schering Corporation v Geneva Pharmaceuticals* case was discussed with the Examiners in the interview, as it was mentioned as the basis for the inherency rejection. Schering is distinguishable from the facts of the instant application. The patent in Schering included 2 claims directed to a compound of DCL (a metabolite of loratadine - Claritin). The court concluded that claims 1 and 3 covering the compound lacked novelty in view of loratadine because the compound was inherently formed in the body. The court specifically found that the other claims directed to pharmaceutical compounds and methods of treating using DCL were not anticipated by loratadine.

On pages 14-15 of the opinion the court specifically stated that claims directed to an isolated compound would not face a similar inherency issue. Each of the pending claims is limited to isolated RNA. The court stated:

> "Finally, this court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known

drugs. Cf. In re Kratz, 592 F.2d 1169, 1174 (CCPA 1979) (stating that a naturally occurring strawberry constituent compound does not anticipate claims to the substantially pure compound); In re Bergstrom, 427 F.2d 1394, 1401-02 (CCPA 1970) (stating that a material occurring in nature in less pure form does not anticipate claims to the pure material).

But those metabolites may not receive protection via compound claims. In this case, for instance, claims 1 and 3 broadly encompass compounds defined by structure only. Such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug. As this case holds, these broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound.

A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in Kratz and Bergstrom, or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

The '716 patent contains claims 5-13 covering pharmaceutical compositions and claims 14-16 covering methods of treating allergic reactions by administering compounds that include DCL. These claims were not found anticipated by the '233 patent."

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Summary

It is believed that the claims are in condition for allowance. A prompt and favorable action is earnestly solicited. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

By: _____

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